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A TH1 POLARIZING VACCINE FOR BOOSTING THE ANTITUMOR ACTIVITY OF ADOPTIVELY TRANSFERRED T CELLS

Song, X.-T.[1], Turnis, M.[1], Zhou, X.[1], Rollins, L.[1], Hong, B.-X.[3], Rabinovich, B.[2], Chen, S.-Y.M.[3], Rooney, C.[1], Gottschalk, S.[1] [1] Baylor College of Medicine, Houston, TX; [2] M.D. Anderson Cancer Center, Houston, TX; [3] University of Southern California, Los Angeles, CA

Background: T cell therapies for several human cancers are showing increasing success, and their effectiveness can be increased by prior lymphodepletion of the host. This process, however, requires intensive chemotherapy or radiation, producing significant morbidity, and mortality. The aim of this project was to develop an adenoviral vaccine to boost the expansion of adoptively transferred T cells without systemic side effects. We show here that a vaccine, which 1) provides antigens, 2) inhibits the antigen presenting attenuator A20, and 3) encodes flagellin for Toll-like receptor (TLR) 5 activation, boosts the expansion and antitumor effects of adoptively transferred T cells in the B16-OVA tumor model.

Methods: Recombinant adenoviruses were constructed that express A20-shRNA to silence A20 (Ad-shA20) or A20-shRNA and flagellin (Ad-shA20-FL). B16-OVA tumor bearing mice were either vaccinated with 1) Ad-shA20-FL/Ad-OVA, 2) Ad-shA20/Ad-OVA, 3) Ad-OVA or 4) Ad-shA20-FL before the adoptive of OVA-specific T cells (OT-I T cells). Routine immunological assays were used to determine the effects of vaccine/T-cell therapy. Bioluminescence imaging was used to track infused OT-I T cells and knockout mice were used for mechanistic studies.

Results: B16-OVA tumor bearing mice were vaccinated on day 5 with Ad-shA20-FL/Ad-OVA, Ad-shA20/Ad-OVA, or Ad-OVA and received a single dose of OT-I T cells on day 7. Only the Ad-shA20-FL/Ad-OVA vaccine induced significant expansion of OT-I T-cells resulting in prolonged regression of B16-OVA tumors. In contrast, injection of OT-I T cells or the Ad-shA20-FL/Ad-OVA vaccine had only modest antitumor effects. Mechanistic studies revealed that Ad-shA20-FL/Ad-OVA vaccination induced robust Th1, Th2, and Th17 responses in B16-OVA bearing mice. Activation of Th1 T cells was critical for the observed effects since the Ad-shA20-FL/Ad-OVA vaccine was ineffective in activating and expanding infused OT-I T-cells in IL12-/- (Th1 deficient) but not in RORγt-/- (Th17 deficient) mice.

Conclusion: This study shows that a TH1-polarizing vaccine efficiently boosts the proliferation and antitumor activity of adoptively transferred T cells obviating the need of lymphodepletion with cytotoxic agents. Hence, this combined vaccine/T-cell therapy should allow the *ex vivo* generation and reinfusion of high affinity T cells against weak tumor antigens thereby broadening the range of tumors that will be susceptible to immune therapy.

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DENDRITIC-CELL BASED TUMOR VACCINATION IN PROSTATE AND RENAL CELL CANCER: SYSTEMATIC REVIEW AND POST-HOC ANALYSIS

Draube, A.[1], Klein-González, N.[1], Rademacher, S.[1], Brillant, C.[2], Hellmich, M.[3], von Bergwelt-Baildon, M.[1] [1] University Hospital of Cologne, Germany; [2] University Hospital of Cologne, Germany; [3] University Hospital of Cologne, Germany

Dendritic cells (DC) as natures adjuvant are a candidate APC for post transplant immune intervention. So far, more than 200 – mostly small phase I/II – clinical trials using DC have been published in cancer. Nevertheless heterogeneity of vaccination strategies, non standardized cellular products and the lack of standard criteria for clinical and immunological responses make it difficult to draw solid conclusions from single trials. Prostate and renal cell cancer (RCC), are regularly infiltrated by antigen-specific immune cells and are considered susceptible to immunotherapy. They have therefore been studied intensively as targets of DC-based interventions. Therefore we chose these entities for a systematic review of DC based tumor vaccines using single patient data to perform comprehensive statistic analyses. We searched the Medline database from January 2000 to December 2007. Articles published with mixed entities, follow-up studies and trials using allogeneic DC were excluded. Twenty four studies in prostate cancer (15) and RCC (9) were analyzed in detail comprising a total of 445 patients.

Available individual patient data of 348 patients were used for post hoc analyses. DC types used for the vaccination strategies were immature monocyte derived DC, mature, monocyte derived DC, and density-grade enriched DC in 8, 12 and 4 studies respectively. For antigen delivery peptides, proteins and tumor lysates were utilized in 33%, 21% and 25% of the patients respectively. Comparison of quality control standards and DC dose revealed striking differences between the studies. Chisquare tests revealed cellular immune response, DC dose and route of vaccination to have a significant influence on the clinical benefit rate (CBR: CR, PR, MR, SD). Analyses stratified by studies confirmed a significant odds ratio for the association of cellular immune response and CBR, and DC dose with CBR, both in prostate cancer and RCC. Taken together, this systematic review disclosed a strong heterogeneity regarding vaccine dose, DC type, antigen delivery, route and quality controls. However, as a 'proof of principle' post-hoc analyses on individual-patient levels revealed an association between the induction of cellular immune response and clinical benefit rate both for prostate cancer and RCC. To our knowledge this is the first systematic review demonstrating statistically significant effects of DC based vaccines further underlining the potential of this treatment strategy.

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH A REDUCED-INTENSITY CONDITIONING REGIMEN (RIST) FOR THE TREATMENT OF SOLID TUMORS: A SINGLE-INSTITUTE EXPERIENCE

Kamiyama, Y.[1], Makimoto, A.[2], Kim, S.-W.[1], Yakushijin, K.[1], Hosono, A.[2], Ueno, N.[1], Fukuhara, S.[1], Hiramoto, N.[1], Asakura, Y.[1], Kurosawa, S.[1], Fukuda, T.[1], Mori, S.[1], Tanosaki, R.[1], Heike, Y.[1], Takaue, Y.[1] [1] National Cancer Center Hospital, Tokyo, Japan; [2] National Cancer Center Hospital, Tokyo, Japan

Objective. RIST has been established as a standard therapy for various hematologic malignancies. However, its feasibility in patients with solid tumors has not been well evaluated, and thus we conducted a single-institute, retrospective study.

Patients and Methods. A total of 44 patients with various advanced solid tumors underwent RIST from a related donor (41 sibling donors; 38 HLA-matched and 6 one-locus-mismatched donors) between April 2000 and August 2006. Most were enrolled in various prospective studies, and efficacy data for colorectal cancer and renal cancer have been published previously (Transplantation 78:1740, 2004; Exp Hematol 32:599, 2004). This follow-up retrospective analysis particularly focused on the overall feasibility of the procedure. The median age of the patients was 43.5 years (range 20-61). Their diseases were renal cell cancer (RCC: 8 mixed cell, 6 clear cell, 2 granular cell and 1 papillary), pancreatic cancer (4), rhabdomyosarcoma (3), colorectal cancer (2), bile duct cancer (2), Bellini duct cancer (2), and others(13). All but one patient, who had PR small cell lung cancer, were in recurrent or primary refractory tumor. The conditioning regimens were Flu (180 mg/m2)/BU(8 mg/kg po)/ATG (Thymoglobulin 5 mg/m2) (19), Flu/BU (10), cladribine(0.66 mg/kg)/BU (9) and cladribine/BU/ATG (6). The primary agent for GVHD prophylaxis was cyclosporine, and 4 patients also received short-term methotrexate.

Results. All patients achieved hematological engraftment at a median of 11 days (range, 6-20). At 30 days and 90 days after transplantation, 10 of the 18 and 10 of the 11 evaluable patients achieved complete donor chimerism. Twenty-one patients developed acute GVHD at a median of 28 days (range, 8-157), including 19 grade 2-4 and 10 grade 3-4. Seventeen developed chronic GVHD at a median of 114 days (range, 94-277). Therapy-related mortality (TRM) was 9% (2 acute GVHD, 1 ARDS and 1 hemorrhagic shock), and 40 died from tumor progression. The median follow-up time was 167 days (range 14-1449). The overall survival rate at 2 years was 11% in the whole group, while patients with RCC (clear cell 33%, all other types 22%) had a higher rate of 25% ($p < 0.0001$).

Conclusion. Although these findings suggest that RIST is feasible in patients with refractory solid tumor, the ultimate usefulness of RIST should be balanced against recently developed promising new agents.